Second-Line Treatment of Small-Cell Lung Cancer

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By John R. Eckardt, MD [2]

Small-cell lung cancer is an aggressive tumor associated with high rates of regional or distant metastases at diagnosis. Although highly chemosensitive to agents given in the first-line setting (eg, etoposide and cisplatin), most patients relapse and have a poor prognosis. Treatment options for relapsed patients include radiotherapy for limited-stage disease and chemotherapy or combined modalities for advanced-stage disease. In clinical practice, however, some oncologists maintain that chemotherapy provides an insufficient survival benefit to justify the sometimes debilitating toxicity associated with the more active regimens in particular. Other potential barriers to further treatment include patient comorbidities, performance status, site(s) of progression, progression-free interval, and previous treatments. However, numerous clinical trials demonstrate that some patients benefit from treatment, achieving prolonged survival, symptom palliation, improved quality of life, and the opportunity, albeit rare, for durable remission. Additionally, several novel chemotherapeutics are available that alone or in combination help patients lead an improved quality of life. Finally, alternative routes and schedules—oral formulations, weekly administration, and prolonged treatment vacations— have been developed to deliver chemotherapy to patients with poor performance status or multiple comorbidities. This article reviews the advantages and disadvantages of treating recurrent small-cell lung cancer and summarizes the utility of several active agents.

ABSTRACT: Small-cell lung cancer is an aggressive tumor associated with high rates of regional or distant metastases at diagnosis. Although highly chemosensitive to agents given in the first-line setting (eg, etoposide and cisplatin), most patients relapse and have a poor prognosis. Treatment options for relapsed patients include radiotherapy for limited-stage disease and chemotherapy or combined modalities for advanced-stage disease. In clinical practice, however, some oncologists maintain that chemotherapy provides an insufficient survival benefit to justify the sometimes debilitating toxicity associated with the more active regimens in particular. Other potential barriers to further treatment include patient comorbidities, performance status, site(s) of progression, progression-free interval, and previous treatments. However, numerous clinical trials demonstrate that some patients benefit from treatment, achieving prolonged survival, symptom palliation, improved quality of life, and the opportunity, albeit rare, for durable remission. Additionally, several novel chemotherapeutics are available that alone or in combination help patients lead an improved quality of life. Finally, alternative routes and schedules—oral formulations, weekly administration, and prolonged treatment vacations— have been developed to deliver chemotherapy to patients with poor performance status or multiple comorbidities. This article reviews the advantages and disadvantages of treating recurrent small-cell lung cancer and summarizes the utility of several active agents.

Despite an unparalleled campaign over the past decade to increase public awareness of risk factors associated with lung cancer, carcinoma of the lung remains the leading cause of cancer-related death in the United States and worldwide.[ 1,2] Epidemiologic data continue to show that lung cancer accounts for 25% and 31% of cancer deaths in women and men, respectively.[ 1] In 2002, over 169,400 new cases of lung cancer were diagnosed and were accompanied by an estimated 154,900 deaths.[1] Although death rates from lung cancer among men decreased for the first time in 1997, death rates among women increased during the same period.
Small-cell lung cancer (SCLC) accounts for approximately 18% of lung cancers and is one of the most aggressive and lethal cancer types.[3] Fiveyear survival rates of SCLC patients with limited disease range from 5% to 10%, and the median survival among SCLC patients with extensive disease is approximately 8 months.[4-6] Although patients typically respond to first-line treatment with systemic chemotherapy (eg, cisplatin plus etoposide), they inevitably relapse. While there are many important determinants of subsequent response in relapsed patients, the prognosis is generally unfavorable, with an unsatisfactory proportion of patients surviving more than 1 year.
To compound matters, many patients in this population are elderly and have multiple comorbidities that may render them unable to tolerate intensive chemotherapy. As a consequence, many oncologists have been reluctant to re-treat these patients and have questioned whether the potential clinical benefits of therapy for recurrent SCLC are sufficient to justify the sometimes debilitating toxicity and psychological stress of repetitive treatments. In this article, the controversies surrounding the treatment of recurrent SCLC patients, including the advantages and disadvantages of chemotherapy, will be reviewed. The review concludes with a summary of several active chemotherapeutics used in this setting.

### Controversies in Recurrent Small-Cell Lung Cancer

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Key Clinical Issues and Considerations in Relapsed SCLC

Many of the clinical issues surrounding recurrent SCLC are derived from a lack of definition of which patient or disease parameters present a sufficient barrier to further treatment, as well as a lack of established criteria to assess clinical benefit. The key clinical issues and controversies related to relapsed SCLC are summarized in Table 1. Major issues include patient survival, symptom palliation, quality of life, and patient selection.

### Survival

In patients who receive best supportive care for recurring advanced SCLC, survival is typically measured in weeks (6 to 8) to several months (approximately 4). Patients who fall into this category generally include those with extensive disease and bulky tumor, and/or poor performance status. Although there has been a lack of large, randomized trials designed to directly compare survival among patients receiving chemotherapy vs best supportive care, observational comparisons have suggested that chemotherapy provides a marked survival benefit.

In the largest randomized study conducted to date in patients with relapsed SCLC, survival was significantly improved in patients receiving short-term chemotherapy (four courses) compared with patients receiving symptomatic treatment (median survival: 20 vs 11 weeks, \( P < .001 \)).\[7\] Other studies of active intervention with chemotherapy in relapsed patients have reported median survivals ranging from 6 to 8 months.\[8-12\] The magnitude of the survival benefit is generally variable and dependent on a number of prognostic factors.

- **Prognostic Factors**—Predictors of survival include performance status, number and location of metastases, and disease-free interval. Survival is clearly improved in patients who have responded to first-line treatment and have experienced a longer progression-free interval (see Patient Selection beginning on page 184). In patients with recurrent SCLC treated with topotecan (Hycamtin), an active, non-cross-resistant topoisomerase I inhibitor approved for recurrent SCLC, median survival in chemo-sensitive patients (ie, progression-free interval > 3 months) ranged from 25 to 36 weeks.\[10-12\] Additionally, in patients who achieved complete response, median survival was 89.5 weeks,\[13\] demonstrating the efficacy and non-cross-resistance of topotecan in patients who responded well to first-line therapy.

In contrast, little progress has been made in re-treating patients who progress on first-line therapy or who otherwise fail to achieve an extended progression-free interval. For instance, in chemoresistant patients with a progression-free interval < 3 months following first-line treatment, median survival is generally comparable or slightly superior to best supportive care (ie, 16 to 21 weeks).\[11,12,14\] In general, this patient group experiences a lower magnitude of survival benefit from re-treatment, and other factors (eg, symptom palliation, quality of survival) should be considered when designing a treatment plan.
In clinical practice, survival is highly variable among relapsed SCLC patients—a proportion of patients will achieve a relatively large survival benefit, whereas others will not. Nevertheless, prolonging survival is an important goal of therapy. In this context, the possibility that patients with unfavorable prognostic factors will not achieve a survival benefit as a result of active treatment should not be the sole rationale for withholding chemotherapy. Other primary considerations for developing a treatment plan include symptom palliation and prolongation of quality survival.

**Symptom Palliation**

For some patients, symptom palliation and quality of life are more important factors in the design of treatment than to what extent treatment may prolong survival. However, despite recognition of the importance of symptom palliation as an outcome in clinical practice, relatively few studies incorporate symptom scores as a component in clinical study design. Additionally, no consensus exists regarding the definitions of symptom palliation, including level and duration of symptom relief, time to palliation onset, and symptom control and prevention.[15] As a consequence, few clinical data exist regarding the potential palliative benefits of chemotherapy in relapsed patients. Despite the dearth of information addressing symptom palliation in SCLC, assessment of symptom palliation has been a focus of some trials. In one large, multicenter, randomized trial comparing symptom palliation (ie, cough) in patients treated with two-drug (etoposide, vincristine) and four-drug regimens (etoposide, vincristine, cyclophosphamide [Cytoxan, Neosar], methotrexate), the four-drug regimen was superior to the two-drug regimen at most time points.[15] When the level of symptom palliation provided by the two regimens was correlated with initial symptom severity, patients presenting with poor symptom scores achieved the most benefit. However, the time to palliation onset and duration of palliation were comparable between regimens.[15]

In another trial comparing topotecan with CAV (cyclophosphamide, doxorubicin [Adriamycin], vincristine), both treatments elicited significant improvements in several general and disease-related symptoms.[16] Additionally, topotecan was superior to CAV in the relief of general symptoms, including anorexia, fatigue, and interference with daily activities, and in the relief of pulmonary symptoms, including dyspnea and hoarseness. Moreover, the time to onset of pulmonary symptoms was delayed (symptoms progressed at a slower rate) in patients receiving systemic chemotherapy.[16]  

**Toxicity Trade-off**—On the other hand, cytotoxic regimens tend to be associated with significant toxicity and morbidity, and patients with poor performance status or elderly patients with multiple comorbidities are often unable to tolerate therapy. Consequently, oncologists and patients are frequently faced with the difficult decision between toxic treatments with intolerable side effects and shorter, but perhaps more tolerable survival without chemotherapy. In addition, although therapy can be customized to improve tolerability, the capacity for these alternative regimens (ie, lower dose levels or frequency) and delivery systems (eg, oral) to ameliorate symptoms has not been established.

An important trade-off to consider when administering one of the more active regimens is the associated toxicity profile. Hematologic toxicity (eg, neutropenia), in particular, is a common toxicity associated with recurrent SCLC treatment. However, myelosuppression is relatively easily managed with the use of growth factors (granulocyte-colony stimulating factor [G-CSF, Neupogen], erythropoietic agents) or adjustments in the dose or frequency of therapy. Other potentially severe toxicities, such as paclitaxel-induced neurotoxicity, can be managed with adjustments in the paclitaxel schedule (24 vs 3 hours) or by switching the patient to an alternative agent.

**Potential Benefits**—A focus on the potential benefits that can be accrued with active treatment and actively intervening in the natural disease course typifies many oncologists' approach to patient management. In addition to palliating existing symptoms, chemotherapy can prevent symptoms from emerging and from progressing to the bone or central nervous system. In patients who achieve complete remission on firstline therapy, prophylactic cranial irradiation provides an additional layer of protection from new metastasis upon relapse.[17] The patients who appear to benefit most are those who enter the relapsed setting as asymptomatic as possible. In patients with a reduced ability to tolerate the demands of chemotherapy, single-agent chemotherapy or supportive care may be the best option. Alternatively, oral formulations, lower dose levels, or less frequent dosing of some agents appears to provide patients with an improved toxicity profile while maintaining efficacy at or near levels observed with standard regimens.[18-20]

**Quality of Life**

A third important consideration when designing a treatment plan for patients with relapsed SCLC is
quality survival. Quality of life is especially important given the median survival of 8 to 9 months associated with currently existing therapies. Similar challenges to those outlined for symptom palliation exist for assessing quality of life. For instance, the precise definition of quality of life varies between centers and over time, and more than 50 distinct instruments have been developed to measure this parameter.[21]

Additionally, although the majority of instruments have been designed to assess changes in disease-related symptom scores, far fewer capture changes in treatment-related symptoms. Consequently, no standards exist, and comparisons across studies are difficult. Nevertheless, quality-of-life assessments are routinely included as important end points in clinical trial design and much information will ultimately be gained regarding the impact of various treatments on patient quality of life.

**Quality-of-Life Indicators**—Estimation of overall patient quality of life generally consists of assessing several interrelated components, including symptom palliation, functional well-being, and psychosocial and emotional concerns. Overall quality of life correlates well with performance status, symptom palliation, and survival.[22-24] These observations are consistent with clinical study results suggesting that physical functioning, treatment-related side effects, disease-specific symptoms, psychological distress, fatigue, and malaise were the best indicators of quality of life in patients receiving chemotherapy.[25,26]

Interestingly, patients appear to experience greater improvements in quality of life while on more intensive regimens, despite experiencing more severe side effects.[27] This finding has been attributed to greater symptom palliation and a slowing in the rate of disease progression with more intensive therapy. However, in studies in which chemotherapy was extended beyond four courses, patients reported a progressive deterioration in their quality of life.[28] These findings illustrate the difficulty of planning treatment and the importance of customizing treatment by balancing all the needs of a given patient.

**Treatment Priorities**—In clinical practice, the quality of life remaining often takes precedence over survival. A satisfactory quality of life can be achieved with standard regimens through symptom palliation and improvement in physical functioning. Further, the relative lack of treatment convenience does not present a significant barrier to treatment, as the majority of patients are willing to sacrifice convenience for the potential benefits of active treatment. The toxicity of therapy presents another impediment to higher quality of life. Many of the serious toxicities associated with active agents are manageable either through pretreatment (eg, antiemetics, antidiarrheals, corticosteroids) and posttreatment (eg, growth factor support) measures as discussed previously, through adjustments in the dose level or frequency, or by initiating treatment with an alternative agent or combination regimen. Finally, although some investigators have suggested that extending treatment beyond four to six courses confers no further survival benefit,[29,30] in clinical practice a proportion of patients clearly benefit from further treatment (to progression), particularly patients with stable disease. Indeed, Cesano et al[13] reported similar survival among relapsed SCLC patients with stable disease and those who achieved a partial response to treatment.

**Patient Selection**

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<tr>
<th>Patient Characteristics Portending Clinical Benefit in Relapsed SCLC Setting</th>
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<td>Progression-free interval &gt; 3 mo following first-line therapy</td>
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<tr>
<td>Performance status &lt; 2</td>
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<tr>
<td>Less bulky disease</td>
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<tr>
<td>Asymptomatic as possible at relapse</td>
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<tr>
<td>No clinically significant comorbidities</td>
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Characteristics of the candidate best suited for systemic chemotherapy in the relapsed setting are
shown in Table 2. Because the majority of patients who enter the clinic do not fall into this category, clinicians tend to customize the treatment plan to meet the needs of each patient. Key patient parameters are reviewed below.

• **Performance Status**—Performance status is a good predictor of quality of life and overall survival in cancer patients.[22,31] The Eastern Cooperative Oncology Group (ECOG) assessment and Karnofsky performance status are two widely used tests that are validated and easily scored. Most oncologists are comfortable treating patients with an ECOG performance status of 0 or 1. Additionally, patients will be eligible for enrollment into clinical trials of novel drug regimens provided their ECOG performance status is good (≤ 2). Importantly, the performance status of patients can often be improved, albeit temporarily, with chemotherapy. In contrast, there is little evidence to suggest that treatment of patients with poor performance status (ECOG 3 or 4) is beneficial. The majority of reports of patients with poor performance status include case studies and subgroup analyses of small numbers of patients from larger trials (protocol violations).[32,33] Patients with poor performance status appear much more likely to die of treatment-related complications.[32] For patients with extensive disease and poor performance status, the potential benefits of therapy must be weighed against potential comorbidities associated with chemotherapy; best supportive care may be a preferable option for selected patients.[34]

• **Comorbidities**—Because a significant percentage of patients with SCLC are long-time smokers and/or elderly, comorbid conditions such as obstructive lung disease, coronary heart disease, arterial hypertension, and diabetes are very common in this population. Any of these conditions can be more serious and take precedence over the treatment of lung cancer. Moreover, impaired end organ function can significantly alter the tolerability profile of cytotoxic agents. For instance, reductions in renal function (serum creatinine > 3 mg/dL) can impede the clearance of cytotoxic agents such as topotecan, thereby increasing patient exposure to various toxicities. Consequently, patients with impaired renal function should receive a lower starting dose of renally excreted agents or, alternatively, receive a non-renal excreted agent (eg, docetaxel [Taxotere], paclitaxel).

Other considerations should be noted for patients with impaired liver function. Cytotoxic agents that are predominantly metabolized in the liver, such as vinorelbine (Navelbine) and docetaxel, can be administered at full dose levels to renally impaired patients. However, hepatically impaired patients will require adjustments in the dose or the use of an altogether different agent that undergoes metabolism elsewhere.

Other important adjustments should be made for patients with cardiac disease and diabetes-two conditions that occur with a higher frequency in SCLC patients. Taxanes are often contraindicated in patients with New York Heart Association class IV congestive heart failure, whereas diabetic patients may worsen from concomitant dexamethasone and taxane therapy.[35]

• **Age**—The single largest influence on comorbidity is patient age. Approximately 66% of lung cancer patients in the United States are over the age of 65 years.[36] Unfortunately, many elderly patients who could benefit from treatment with singleagent or combination regimens are undertreated. Additionally, there has been reluctance on the part of oncologists to enroll older patients in clinical trials. This undertreatment has continued despite evidence that advanced age alone has not been found to be an independent predictor of reduced survival in SCLC.[37] Nevertheless, elderly patients (> 70 years old) or patients with poor performance status (ECOG > 2) do not tolerate chemotherapy as well as younger patients or patients with ECOG performance status scores ≤ 2. Comorbid conditions and impaired organ function contribute to this intolerability. Consequently, elderly patients are more susceptible to neurotoxicity or myelosuppression, the latter attributed to a reduction in bone marrow cellularity. Platinum-based regimens are usually avoided in this patient population because the associated renal and neurotoxicities can exacerbate preexisting comorbidities. As a result, single-agent chemotherapy has been investigated for use in these patient populations. These non-platinum-based agents provide clinical benefit with improved quality of life. Platinum-based regimens are usually avoided in this patient population because the associated renal and neurotoxicities can exacerbate preexisting comorbidities. As a result, single-agent chemotherapy has been investigated for use in these patient populations. These non-platinum-based agents provide clinical benefit with improved quality of life.

The best course of treatment for an individual patient must factor in the patient's quality of life. Therefore, non-platinum-based treatments (single agent or in combination) that provide clinical benefit with less toxicity need to be further developed.[38] Finally, supportive measures alone are often the best option for elderly patients with poor performance status (ECOG > 2).
• **Progression-Free Interval**—The progression-free interval is an important predictor of subsequent response to chemotherapy in the recurrent setting. A progression-free interval in patients with relapsed SCLC that exceeds 3 months is a harbinger of beneficial response to subsequent treatment with the same agent(s) and, alternatively, with non-cross-resistant agents. In clinical trials, chemo-sensitive patients characterized by a progression-free interval > 3 months achieve a significantly greater overall response rate and a longer survival compared with chemo-resistant patients.[10-14,16]

In contrast, patients who experience refractory disease or disease progression while on therapy should be considered for re-treatment with non-cross-resistant chemotherapy or new agents, or, alternatively, discontinued and provided best supportive care. Although no randomized study to date has reported on the magnitude of symptom and quality-of-life benefits that chemorefractory patients may achieve from systemic chemotherapy, in clinical practice some patients clearly benefit through the slowing of disease progression and the provision of symptom palliation.

**Role of Chemotherapy in Recurrent SCLC**

The introduction of each successive generation of chemotherapeutics over the past 4 decades has led to incremental shifts in the clinical approach to lung cancer treatment. As the efficacy and survival impact of chemotherapy have improved, the goals of therapy have evolved from providing best supportive care for the last few months of life, to providing active intervention in the natural history of the disease. Further development and refinement of novel combinations and schedules have continued to drive interest among oncologists in treating their patients with an important focus on symptom palliation, regimen tolerability, and quality of life. TABLE 3

**Table 3: Characteristics of Active Agents in Relapsed Small-Cell Lung Cancer**

Patients who relapse are candidates for second-line or salvage chemotherapy, provided they meet the general selection criteria summarized above. Several novel chemotherapeutic agents have shown activity in SCLC (Table 3),[10-12,14,16,39-50] including topoisomerase I inhibitors (eg, topotecan, irinotecan [CPT-11, Camptosar]), semisynthetic vinca alkaloids (eg, vinorelbine), novel antimetabolites (eg, gemcitabine [Gemzar]), and members of the taxane family (eg, docetaxel, paclitaxel).

Many of the more active agents employed in second-line treatment (eg, topotecan, irinotecan, docetaxel, vinorelbine) are non-cross-resistant to first-line therapies. They exhibit novel mechanisms of action relative to cisplatin/carboplatin and etoposide, thereby targeting a different aspect of cell division. Additionally, many of these agents have shown synergy with other agents (both second- and first-line agents) in tumor model studies, thereby providing the rationale for their use in various combination regimens.

**Topotecan**

Topotecan is an established treatment in recurrent SCLC, with tumor response rates of 2% to 31% reported in patients who have extensive disease but good performance status (ECOG ≤ 2).[10-12,14,16] In platinum-sensitive patients (progression-free interval ≥ 3 months), overall tumor response rates have ranged from 11% to 31%, whereas in platinum-refractory patients, overall response rates are between 2% and 7%.[10-12,14,16] An additional 18% to 30% of platinum-sensitive and 4% to 23% of platinum-refractory patients treated with topotecan achieve stable disease. Median survival ranges from 25 to 36 weeks in platinum-sensitive and 16 to 21 weeks in platinum-refractory SCLC patients. In one analysis, the median survival in patients who experienced a complete response was 89.5 weeks (hazard ratio = 0.141 vs nonresponders).[13] Significant benefits in the palliation of disease-related symptoms have been observed with topotecan.[10,16] In a phase III trial of topotecan vs CAV in patients with recurrent SCLC, topotecan...
was associated with significant improvements in general symptoms (P < .05), including anorexia, fatigue, and interference with daily activity, and pulmonary symptoms, including dyspnea and hoarseness. Additionally, topotecan treatment significantly slowed the progression of dyspnea (P = .046) and anorexia (P = .003).[16]

In a similar study comparing oral and intravenous topotecan,[10] more than 20% of patients in both treatment arms reported improvement at consecutive visits in chest pain, hemoptysis, insomnia, hoarseness, and interference with daily activity. The activity, tolerability, and symptom improvement results of these trials establish the clinical value of topotecan in second-line therapy of SCLC. A number of trials are ongoing or planned to evaluate novel topotecan-based combination regimens (eg, topotecan plus paclitaxel) and different doses, schedules (3-day, weekly), and routes of delivery (ie, oral).

**Irinotecan**

Although irinotecan is licensed for metastatic carcinoma of the colon, the results of several small studies have suggested activity in relapsed SCLC. The agent has primarily been evaluated in combination regimens in small studies[51]; in particular, combination therapy with irinotecan and cisplatin has emerged as a potentially active regimen in SCLC.[52] In studies of irinotecan plus cisplatin, overall response rates of 47% (7/15)[51] and 78% (18/23)[53] have been reported in relapsed or refractory SCLC patients. In one study, median survival was 251 days.[53]

The single-agent activity of irinotecan in previously treated SCLC patients was modest in one study, with a reported overall response rate of 14%.[39] Preliminary results from another investigation demonstrated overall response rates of 35% and 4% for chemosensitive and chemoresistant relapsed SCLC patients, respectively.[40]

**Vinorelbine**

Although the majority of clinical experience with vinorelbine is in the non-small-cell lung cancer (NSCLC) setting, the agent has demonstrated activity in SCLC. In a single-agent study of vinorelbine, 3 (12.5%) of 24 heavily pretreated SCLC patients achieved partial responses.[41] Another study of vinorelbine as singleagent therapy reported partial responses in 4 (16%) of 25 previously treated SCLC patients.[42]

Vinorelbine-based combination regimens have been evaluated most extensively in NSCLC and would appear to offer better overall responses, compared with single-agent therapy in SCLC. In a phase I feasibility study of vinorelbine and paclitaxel in previously untreated patients, the overall response rate was 32% (7/22), including one complete response.[54] No studies to date have reported on the potential effects of vinorelbine on symptom palliation or prevention in SCLC patients. Additional, welldesigned trials will be needed to determine the place of vinorelbine in salvage therapy of SCLC.

**Gemcitabine**

Gemcitabine has demonstrated activity in the SCLC salvage setting and is under investigation in this area. In a study in heavily pretreated patients (two previous regimens) refractory to their most recent treatment, gemcitabine was associated with five partial responses (13%) in 38 evaluable patients.[44] In another study of gemcitabine at first relapse, five partial responses (four in sensitive and one in refractory patients) were observed in 43 evaluable patients, for an overall response rate of 12%.[43]

The potential role of gemcitabine-based combinations has also been evaluated in SCLC. A recent phase II trial evaluated the second-line antitumor activity of gemcitabine with paclitaxel.[55] Although the evaluable group was limited to 20 patients, 60% of sensitive and 40% of refractory SCLC patients achieved objective responses. No complete responses were observed. Although this agent has demonstrated varying degrees of antitumor activity in SCLC, more data are needed, particularly regarding patient survival and impact on general and disease-specific symptoms.

**Docetaxel**

Docetaxel is indicated in the treatment of NSCLC. In a study by Smyth et al,[45] seven partial responses (25% response rate) were observed in 28 previously treated SCLC patients receiving docetaxel at 100 mg/m². The duration of response ranged from 3.5 to 12.6 months. In a recent pilot study of docetaxel administered at the maximal tolerated dose (in Japan) of 60 to 70 mg/m², 3 of 10 patients treated in the salvage setting achieved objective responses (one complete response, two partial responses).[46] However, all responses were seen in patients with limited-stage disease. To
date, no survival data appear to be available for docetaxel in this setting. In summary, although docetaxel is an important therapy in first-line treatment of various solid tumors, a role in salvage therapy of SCLC has yet to be established. Additionally, randomized studies will be needed to clarify the potential role of docetaxel in recurrent SCLC, including quality-of-life effects such as symptom palliation.

**Paclitaxel**

Paclitaxel is indicated in the first-line treatment of NSCLC. Several smaller studies have been published on the antitumor activity of paclitaxel-based regimens in recurrent SCLC.[47,48] In a study by Kakolyris et al.[47] seven partial responses and one complete response (25% overall response rate) were observed in 32 previously treated patients receiving paclitaxel 200 mg/m² and carboplatin at an area under the concentration-time curve (AUC) of 6. All but one responder had received previous treatment with etoposide and cisplatin. Median duration of response was 3 months, and the time to progression was 5.5 months.[47]

In another study of paclitaxel and carboplatin, among 34 previously treated, mixed-stage SCLC patients, 23 achieved a partial response and 2, a complete response.[48] Median time to progression was 4.8 months, with a median survival of approximately 7.2 months. Only 9% of patients were alive at 1 year.

In summary, a role for paclitaxel in salvage therapy of SCLC has yet to be established in randomized trials. Additional studies will be needed to determine the impact of paclitaxel on patient quality of life and symptom palliation.

**Cyclophosphamide, Doxorubicin, and Vincristine**

The combination of cyclophosphamide, doxorubicin, and vincristine has been used for some time in relapsed SCLC patients.[49,50] Second-line or salvage therapy with CAV has been associated with overall tumor response rates of 13% to 28% and median response durations ranging from approximately 15 to 26 weeks.[16,49,50] In a larger, randomized trial of 104 patients, the overall response rate was 18% and the median survival was 25 weeks. Approximately 14% of patients with relapsed SCLC receiving CAV were alive at 1 year. Disease-related symptom improvement (two consecutive improvements over baseline assessment) during therapy was limited. Improvements in dyspnea, fatigue, anorexia, and interference with daily activity were reported in 7%, 9%, 16%, and 11% of patients, respectively.

In summary, CAV continues to serve as a benchmark comparator in SCLC trials and represents a useful option in the second-line treatment of SCLC. However, compared with CAV, other treatment options appear to offer improved tolerability and symptom control.[16]

**Conclusions**
Limitations associated with current treatment options have prompted a continued evolution in the goals of therapy such that today, oncologists in general attempt to strike a balance between the patient's needs for tumor response, survival, and quality of life. In this context, improvements in palliative treatment and in prolonging quality survival have become major goals of therapy. These critical goals must often be balanced against the toxicity of the schedule and the impact on patient quality of life.

Although there is a clear need for new agents and combinations, patients can achieve measurable benefits with existing therapies. Indeed, the SCLC field is epitomized by a very active investigation of

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a myriad of novel combinations, unique schedules, and routes of administration, all with the aim of improving patient outcomes. These treatments can extend survival, provide symptom palliation and accompanying quality-of-life benefits, and provide comfort to patients in that they are addressing the disease in a positive manner.

Of the active agents currently available for second-line treatment of SCLC, topotecan is the best characterized. Topotecan alone and in combination with other agents provides good tumor response rates and marked symptom palliation, with a well-characterized, noncumulative, and manageable toxicity profile. Future gains in patient outcomes are eagerly awaited by patients and oncologists alike as new agents and novel combinations and delivery systems are introduced into clinical practice.

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